Center for Biologics Evaluation and Research

Report to the Biologics Community

1999

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

CBER's Mission

… is to protect and enhance the public health through regulation of biological products including blood, vaccines, therapeutics, and related drugs and devices, according to statutory authorities…

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From the Director

Center for Biologics Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

(Date)

Dear Colleague in the Biologics Community:

I am pleased to provide the third annual *Report to the Biologics Community* from the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER). This report provides highlights from CBER's activities during Fiscal Year 1999.

During FY 1999, CBER approved the first genetically engineered treatment for rheumatoid arthritis, a drug that blocks a protein that causes the inflammatory disease. Also approved, was a drug designed to prevent graft rejection in kidney transplant recipients, as well as the first biologic for the clotting disorder, von Willebrand's Disease, and the first vaccine to aid in the prevention of Lyme disease. It was a productive year, with the approval of 71 new product license applications and over a thousand supplements.

The 21st century promises significant challenges for CBER. Those challenges include reducing drug development time and addressing the regulation of new and emerging therapies and technologies including human tissue, xenotransplantation, genomics and gene therapy, as well as embryonic stem cells. These challenges must be addressed within the higher performance goals identified in PDUFA II. To date, CBER has met or exceeded the performance goals which began in FY 1994.

We look forward to working with you and another productive year in FY 2000. If you have any questions regarding this report, please contact me at (301) 827-0548.

Sincerely,

Kathryn C. Zoon, Ph.D.
Director
Center for Biologics Evaluation and Research
Food and Drug Administration

Approval Highlights

Biological Products Regulated by CBER

Vaccines

Blood Derivatives

Allergenic Extracts

Blood Components

Whole Blood

Tissues

Monoclonal Antibodies

Biotech Derived Products

Somatic Cell and Gene Therapy

In Vitro Diagnostics

Medical Devices

Arthritis

On November 2, 1998, FDA licensed the first genetically engineered treatment for rheumatoid arthritis – a drug that blocks a protein that causes the inflammatory disease. This incurable disease occurs when the body's immune system mistakenly turns against the joints.

Etanercept, marketed under the trade name Enbrel, will offer an alternative to the more than two million Americans who suffer from rheumatoid arthritis (RA). Etanercept helps reduce moderate or severe symptoms in patients with active RA who have not responded well to other treatment. It can also be used in combination with Methotrexate if patients do not benefit enough from use of Methotrexate alone.

Of the approximately two million Americans with RA, as many as a third to a half of these people are estimated to have moderate to severe RA. The disease occurs when patients' immune systems go awry and attack their joints, causing inflammation and stiffness as rogue immune cells eat away cartilage and eventually erode their bones. Within 10 years, approximately half the patients are too disabled to work. It can strike at any age, but usually appears between the ages of 20 and 50; affecting mostly women.

Enbrel is the first in a new class of rheumatoid arthritis drugs known as biological response modifiers. The new product binds to tumor necrosis factor (TNF), a naturally occurring protein in the body, and inhibits its action. TNF, which promotes

inflammation in the body, is found at elevated levels in the fluid surrounding the affected joints of RA patients.

CBER Product License Applications Received
FY96-99

Fiscal Year	Biotechnological Products			Blood/ Source Plasma	Other*	Total
	Therapeutic	Vaccine	In Vitro Diagnostic			
96	6	0	2	22	11	41
97	10	1	7	29	16	63
98	11	0	3	35	30	79
99	4	3	3	42	12	64

* Other includes Non-Biotech Vaccines, Therapeutics, Allergenics and In Vitro Diagnostics

Etanercept is marketed by Immunex Corporation, Seattle, Washington, and Wyeth Ayerst Laboratories, Philadelphia, Pennsylvania.

Renal Transplant Drug

FDA approved Thymoglobulin, a drug used to aid in the treatment of acute rejection in renal transplant patients, on December 30, 1998. Thymoglobulin is a polyclonal antibody designed to prevent graft rejection in kidney transplant recipients.

FDA approval followed a 163-patient Phase III clinical trial in which the drug successfully reversed acute organ rejection in 78% of kidney transplant patients.

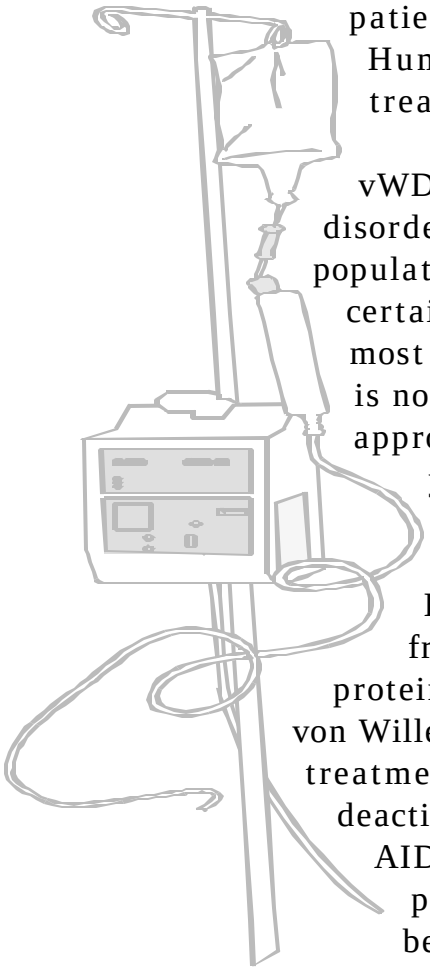
Thymoglobulin is manufactured by Pasteur Meriex Serums of Lyon, France.

Von Willebrand's Disease

FDA approved the first biologic for the clotting disorder, von Willebrand's (vWD) Disease, on April 1, 1999. The new indication for a plasma-derived product called Antihemophilic Factor/von Willebrand Factor Complex (Human), is marketed as Humate-P. Humate-P has been approved for use in adult and pediatric patients for the

treatment of spontaneous and trauma-induced bleeding episodes in severe vWD and in mild and moderate cases where use of desmopressin is known or suspected to be inadequate.

Currently, another drug, desmopressin, is an effective treatment for some forms of vWD. But for about 600 patients, plasma-derived products are needed. Humate-P is the only approved plasma-derived treatment for vWD.



vWD is the most common hereditary bleeding disorder. It affects approximately 1% of the U. S. population. It is caused by a deficiency or defect in certain plasma proteins critical to blood clotting. In most people the disease is mild and usually treatment is not required to control the bleeding. However, approximately 2,000 people in the United States each year suffer from severe forms of vWD. In these cases bleeding can be excessive if not treated.

Humate-P is purified from pooled human plasma from many donors and contains the clotting proteins deficient or defective in vWD, factor VIII and von Willebrand factor. It is pasteurized by heat treatment, a highly effective FDA approved process for deactivating many viruses that cause disease, including AIDS and certain types of hepatitis. In addition, plasma donors are screened carefully. However, because the product is made from human plasma, the risk for transmission of blood-borne viruses, while very low, cannot be totally eliminated.

Prior to this additional approval, Humate-P has been approved to treat adult patients with hemophilia A.

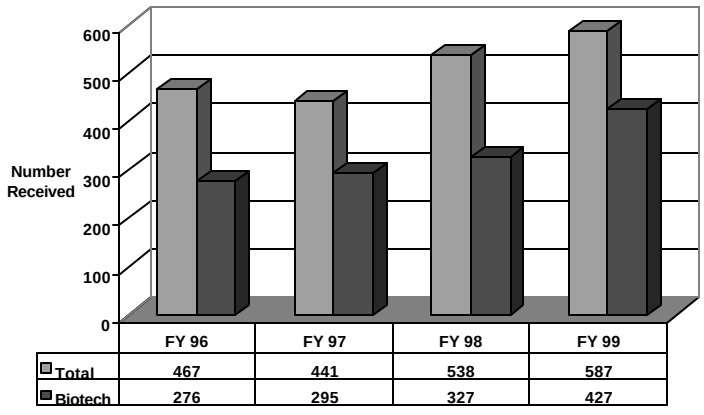
Humate-P is a product of Centeon Pharma GmbH and is distributed by Centeon L.L.C. of Kankakee, Illinois.

Focus on FY 1999

Medical Device Action Plan

On April 26, 1999, the Medical Device Action Plan was signed. The plan facilitates the implementation of the device provisions of the Food and Drug Administration Modernization Act (FDAMA) and assures consistency of policy and procedures between CBER and CDRH. It assesses any differences that may exist and determines if those differences are justified in the interest of public health. This plan addresses areas of cooperation, coordination, and communication between CBER and CDRH to assure harmonized activities. It focuses on Center review practices and performance goals under a managed review process. The plan also includes ongoing research activities to maintain input and feedback from industry and the public. The general principles of the plan require further development by CBER and CDRH to work out specific details.

INDs/IDEs Received in CBER FY 96 - 99
Biotech and Total



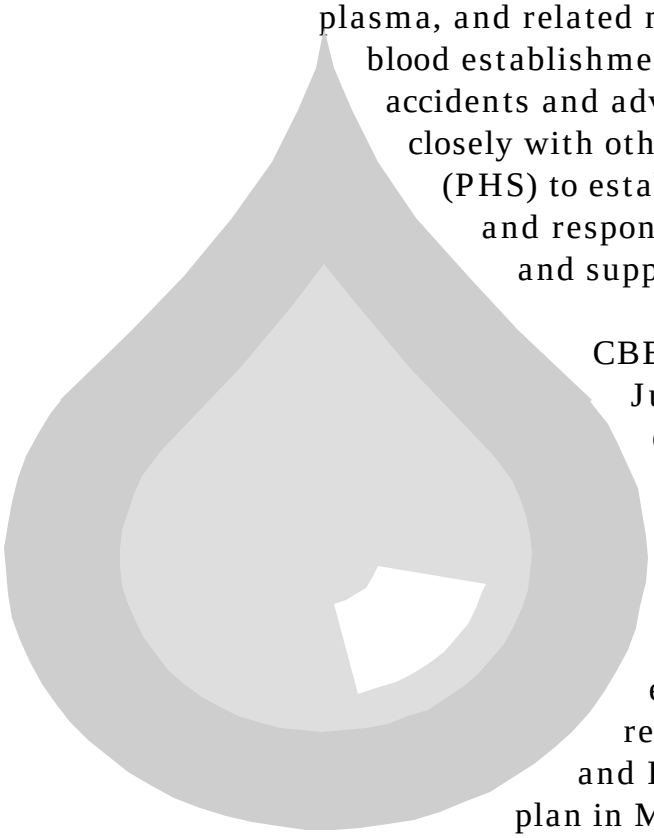
	FY 96	FY 97	FY 98	FY 99
Total	467	441	538	587
Biotech	276	295	327	427

When enacted in 1997, FDAMA made several significant changes to the regulation of medical devices. CBER regulates medical devices related to licensed blood and cellular products by applying appropriate medical device laws and regulations. The regulated medical devices are associated with blood collection and processing procedures as well as cellular therapies. CBER has developed specific expertise in blood, blood products and cellular therapies. The integral association of certain medical devices with biological products supports the regulation of those devices by CBER.

The Nation's Blood Supply

Blood Action Plan

FDA/CBER is responsible for regulatory oversight of the U.S. blood supply. FDA promulgates and enforces standards for blood collection and for the manufacturing of blood products, including both transfusible components of whole blood, pharmaceuticals derived from blood cells or plasma, and related medical devices. FDA also inspects blood establishments and monitors reports of errors, accidents and adverse clinical events. CBER works closely with other parts of the Public Health Service (PHS) to establish blood standards, and to identify and respond to potential threats to blood safety and supply.



CBER initiated a Blood Action Plan in July 1997, to increase the effectiveness of its scientific and regulatory actions, and to ensure greater coordination with our PHS partners. The Action Plan addresses highly focused areas of concern such as emergency operations, response to emerging diseases, and updating of regulations. The Department of Health and Human Services (HHS) accepted this plan in March 1998. The plan is being jointly implemented by CBER, other FDA components (i.e., Office of Regulatory Affairs, Office of Chief Counsel), the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Health Care Financing Administration (HCFA).

The Blood Action Plan involves several initiatives. The initiatives are: updating the blood regulations; the reinvention of blood regulations; addressing emerging infectious diseases; ensuring compliance of plasma

fractionation establishments; blood donor/recipient notification and lookback, and FDA emergency and Class I recalls affecting blood safety response procedures. CBER has completed its systematic update of the blood regulations. The number of exemptions to outdated blood regulations has been reduced. The number of guidance documents lacking enforceability has been reduced, and the blood industry's compliance with standards has been increased. In addition, Team Biologics has been established to ensure continued compliance.

Implementation of the Blood Action Plan has greatly improved the regulatory oversight and safety of the nation's blood supply.

Mad Cow Disease and Its Possible Effects On the Blood Supply

The Food and Drug Administration imposed a ban on August 17, 1999, on blood donations by anyone who has traveled to or lived in Britain for a total of six months between January 1980, and December 1996. Some Americans who frequently traveled to Britain during that country's mad cow disease crisis are temporarily deferred from donating blood in the United States - - a restriction that may reduce the United States' blood supply during a critical time of shortage, but one the government feels is a necessary precaution.

The donor ban is a precautionary measure; there is no evidence that any mad cow-related illness has been spread through blood transfusions. Still, the FDA's donor ban is controversial.

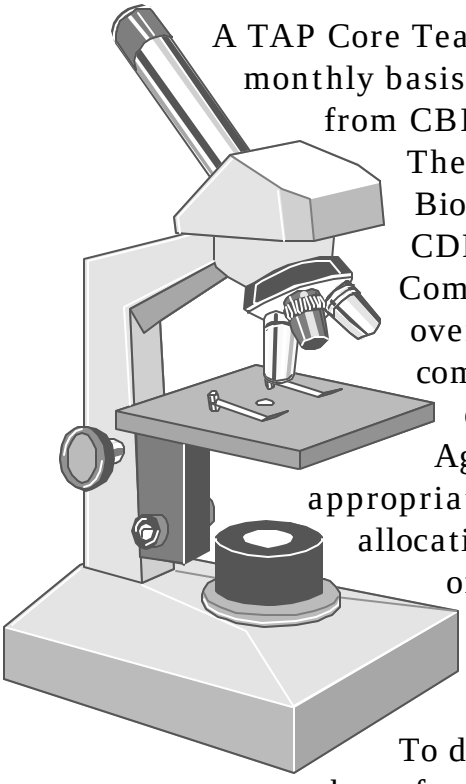
A statistical report conclusion presented to the Transmissible Spongiform Encephalopathies (TSE) Advisory Committee suggested that the ban will reduce the United States' blood donations by 2.2 percent at a time when the demand is increasing. To address the possible shortfall, the FDA is leading an interagency PHS talk-

group. A plan has been developed to monitor and increase the blood supply. This plan has been adopted as part of the Blood Action Plan.

Cellular and Tissue-Based Products

Tissue Action Plan

The Tissue Action Plan (TAP) was implemented in March, 1998. The purpose of the TAP is to develop on a timely basis the policies, regulations and guidance documents needed to implement the "Proposed Approach to the Regulation of Cellular and Tissue-based Products" announced by FDA in February of 1997, and the steps that FDA agreed to take in response to the recommendations made in the GAO's December 1997 report, "Human Tissue Banks: FDA Taking Steps to Improve Safety, but Some Concerns Remain."



A TAP Core Team was formed that meets on a monthly basis. It is composed of representatives from CBER's Offices of the Director, Blood, Therapeutics, and Compliance and Biologics Quality, as well as from CDRH, and the Office of the Commissioner. The Core Team oversees the progress of the commitments of the TAP, communicates progress to the Agency and other organizations as appropriate, and addresses resource allocation issues. It also makes decisions on significant policy issues and provides final review and sign-off on TAP deliverables.

To date, eleven TAP task groups have been formed and meet on a routine basis.

Several of these task groups are responsible for regulation and guidance development. The purpose of other groups includes exploring policy development in specialized areas such as compliance and inspections, reproductive tissues and ancillary products. These task groups have established milestones and report directly to the Core Team on their progress.

One of the TAP task groups is the Tissue Reference Group (TRG). The purpose of the TRG is to provide a single reference point for product specific questions received by FDA (either through the Centers, or from the Office of the Chief Mediator and Ombudsman (OCMO)) concerning jurisdiction and applicable regulation of human cellular and tissue-based products. The TRG gives recommendations to the Centers and to OCMO, which then communicate with the sponsor.

The TRG is composed of six representatives: three from CBER and three from the Center for Devices and Radiological Health (CDRH). Also attending meetings is a liaison from the OCMO and the executive secretary. The TRG was created in February, 1997, and currently meets twice a month.

Listed below are the FY 99 significant accomplishments in this area:

- To assist FDA investigators of tissue products, a list of tissue products regulated by CDRH and CBER was made publicly available on December 1, 1998.

- On March 10, 1999 CBER published TAP Internet and Intranet web pages.

- The publication, Import Alert #57-08, Human Tissue Intended for Transplantation (updated on June 7, 1999), was made available on the TAP Internet web page.

- Publication of a proposed regulation, "Suitability Determination for Donors of Human Cellular and Tissue-based Products" on September 30, 1999.

- The TRG made recommendations on the regulatory approach to be applied to two new products.

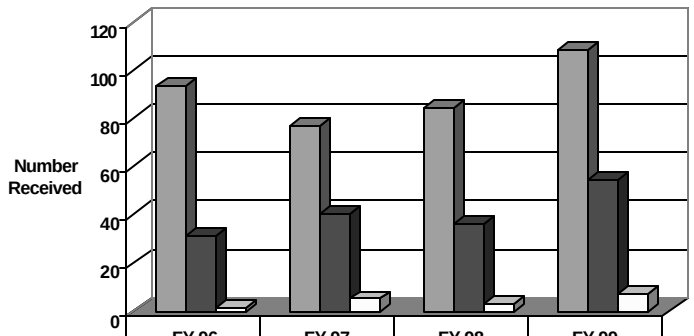
-One involved processing by methods that changed tissue function or characteristics with a metabolic mode of action and hence the product was considered a biologic.

-One consisted of *ex-vivo* expanded hematopoietic stem cells and, hence, is considered a biologic product.

Xenotransplantation Action Plan

In 1994, CBER received its first investigational new drug applications in the area of xenotransplantation. Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a non-human animal source, or (b) human body fluids, cells, tissues or organs that have had *ex-vivo* contact with live non-human animal cells, tissues or organs.

Somatic Cell/Gene Therapy INDs/IDEs received by CBER FY 96 - 99



	FY 96	FY 97	FY 98	FY 99
Somatic Cell	93	77	84	108
Gene Therapy	31	40	36	54
Xenotransplantation Prod.	1	5	3	7

While xenotransplantation holds the promise of providing new therapeutic options as well as the long-term potential of overcoming the current organ shortages, CBER staff recognized that transplantation of non-human live cells also presents a risk of introducing infectious diseases into the human population. FDA/CBER initiated a Xenotransplantation Action Plan as

a result of these potential health risks.

Listed below are a few of the significant accomplishments in FY 1999 in the area of xenotransplantation:

- The Notice of Availability, "Guidance For Industry: Public Health Issues Posed by the Use of Non-Human Primate Xenografts in Humans" was published in the *Federal Register* on April 6, 1999. This document, issued for immediate implementation, recommends that non-human primates not be used as sources of xenotransplantation products until more information is available to assess safety.

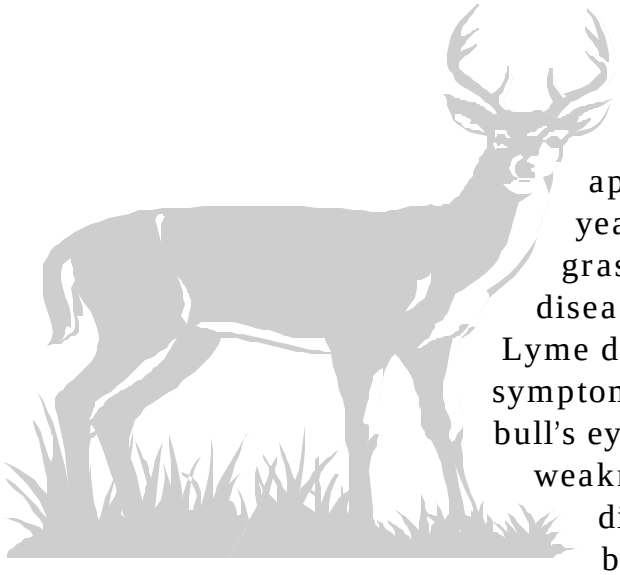
- The second meeting of the Xenotransplantation Advisory Subcommittee of the Biological Response Modifiers Advisory Committee (BRMAC) was held on June 3-4, 1999. This meeting updated the subcommittee and the general public on the development of FDA policy on xenotransplantation and on issues of screening and testing of xenografts and recipients for porcine endogenous retrovirus (PoEV). Brief discussions were held regarding newly identified zoonotic porcine viruses, such as the Hendra-like virus in Malaysia. FDA requested discussion and advice on whether different categories of xenografts, or use in different patient populations, present different levels of risk to the public health. FDA also requested that the subcommittee discuss infectious disease and immunologic issues, as well as the appropriate clinical indication for use of a whole organ xenograft in humans.

Recently, CBER xenotransplantation research has broadened to address the biology of porcine endogenous retroviruses in order to aid in risk assessment, as well as experiments assessing the effects of immune response in xenotransplantation and how that may effect the safety and efficacy of pig to human transplantation.

Developments in Vaccines

Lyme Disease

FDA licensed the first vaccine to aid in the prevention of Lyme disease on December 21, 1998. Lyme disease is transmitted to people through the bites of ticks infected with the bacterium Borrelia burgdorferi. The new vaccine LYMErix, is approved for use in people 15 to 70 years of age who live or work in grassy or wooded areas where Lyme disease-bearing ticks are present. Lyme disease produces a wide range of symptoms, from a rash in the shape of a bull's eye and flu-like problems to facial weakness and heart abnormalities. If diagnosed early, patients can usually be treated successfully with antibiotics. However, if left untreated, Lyme disease can severely damage the heart and nervous system.



Lyme disease is caused by a bacterium carried by pin-sized ticks that live in grassy and wooded areas nationwide, but especially in the Northeast and upper Midwest. Approximately 13,000 confirmed cases of Lyme disease were reported to CDC in 1997. About one-third of the reported cases are in children.

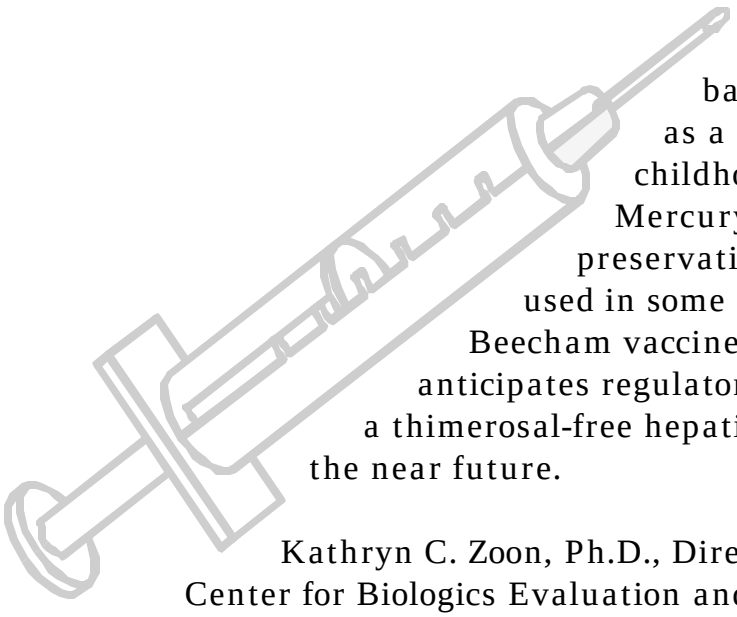
The vaccine was given to healthy individuals, and was generally well tolerated. Local injection site reactions, including redness, soreness, and swelling, were common. Most other adverse events, such as flu-like symptoms and muscle and joint pain, occurred less frequently and were mild to moderate. Although LYMErix may provide protection for a majority of people, it does not prevent all cases of Lyme disease.

LYMErix is marketed by SmithKline Beecham Pharmaceuticals of Philadelphia, Pennsylvania.

NVAC-Sponsored Workshop on Thimerosal

On August 12, 1999, CBER participated in the National Vaccine Advisory Committee (NVAC) – sponsored workshop on thimerosal for vaccines.

The workshop was convened to examine ways to reduce or eliminate the use of mercury-based thimerosal as a preservative in childhood vaccines. Mercury-free preservatives are already used in some SmithKline Beecham vaccines and Merck anticipates regulatory submission of a thimerosal-free hepatitis B vaccine in the near future.

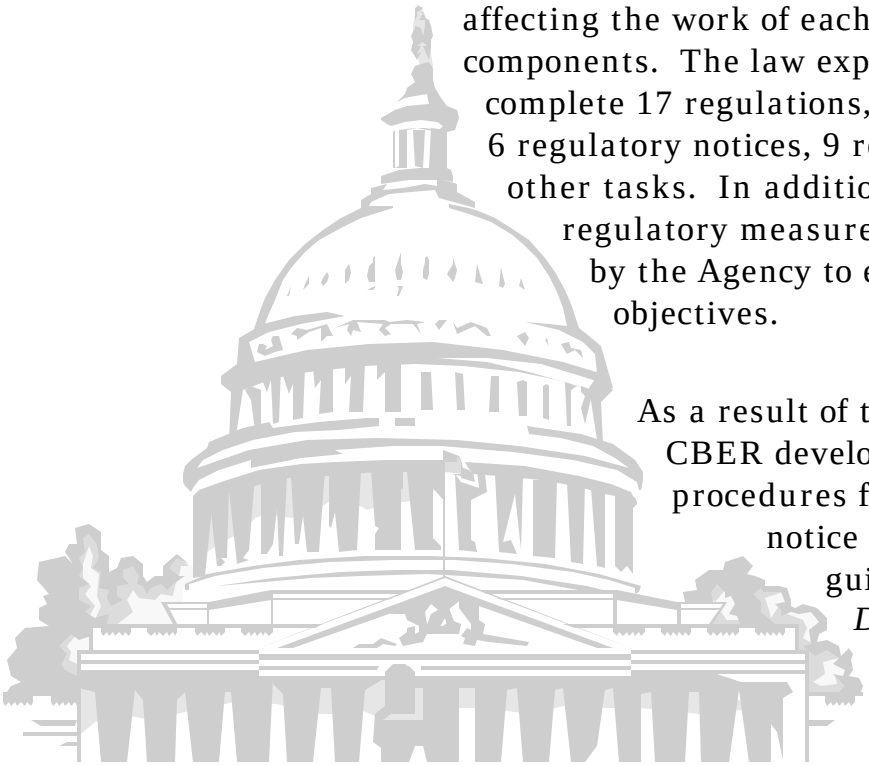


Kathryn C. Zoon, Ph.D., Director of FDA's Center for Biologics Evaluation and Research stated, "Characterization of thimerosal's effects in vaccinated children should constitute a significant portion of immediate research, balanced with research into new types of vaccine preservatives."

FDAMA and PDUFA II

Food and Drug Administration Modernization Act

The Food and Drug Administration Modernization Act of 1997 (FDAMA) is a wide-ranging piece of legislation affecting the work of each of the Agency's key components. The law explicitly required FDA to complete 17 regulations, 11 guidance documents, 6 regulatory notices, 9 reports and at least 18 other tasks. In addition, scores of other regulatory measures were deemed necessary by the Agency to effectively meet the law's objectives.



As a result of the FDAMA requirements, CBER developed the policies and procedures for fast track products. A notice of availability for guidance (*Fast Track Drug Development Programs - Designation, Development and Application Review*) on these policies and procedures was published in November 1998, within one year of Act enactment. The guidance informs sponsors of a new product intended for the treatment of a serious or life-threatening condition which demonstrate the potential to address unmet medical needs that they may request the Agency to designate the application as fast track, and the Agency will respond to the request within 60 days. Product development programs that receive fast track designation may apply for permission to submit portions of an incomplete application for review ("rolling review") at the appropriate time in development. The section also codifies the accelerated approval regulation provision.

Prescription Drug User Fee Act II

FDAMA, Public Law 105-115, authorized revenues from fees paid by the pharmaceutical industry to expedite review by the FDA of human drug applications. These revenues are directed by section 101(4) of this Act toward accomplishment of goals identified in the letters of November 12, 1997 from the Secretary of Health and Human Services to the Chairman of the Energy and Commerce Committee of the House of Representatives, and the Chairman of the Labor and Human Resources Committee of the Senate.

The additional resources are to be used to expedite the review process for human drug and biologic applications so that prescription drug and biological products can reach the market more quickly. Excluded products include: allergenic extract products; whole blood or a blood component for transfusion; *in vitro* diagnostic biologic products; a bovine blood product for topical application licensed before September 1, 1992; large volume parenterals approved before September 1, 1992; a biological product that is licensed for further manufacturing use only, and a large volume biological product intended for single dose injection for intravenous use or infusion. Excluded process activities include: enforcement policy development; post-approval compliance and surveillance activities, including review of adverse drug reports and annual reports; advertising review activities once marketing of the product has begun; inspections unrelated to the review of covered applications; and research.

The FY 99 cohort review performance goals were:

- Review and act on 90 percent of standard original NDAs and PLAs/BLAs filed during FY 99 within 12 months of receipt and review and act on 30 percent within 10 months of receipt.

- Review and act on 90 percent of priority original NDA and PLA/BLA submissions filed during FY 99 within 6 months of receipt.

- Review and act on 90 percent of standard efficacy supplements filed during FY 99 within 12 months of receipt and review and act on 30 percent within 10 months of receipt.

- Review and act on 90 percent of priority efficacy supplements filed during FY 99 within 6 months of receipt.

- Review and act on 90 percent of manufacturing supplements filed during FY 99 within 6 months of receipt and review and act on 30 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

- Review and act on 90 percent of Class 1 resubmitted original applications filed during FY 99 within 4 months of receipt, and review and act on 50 percent within 2 months of receipt.

- Review and act on 90 percent of Class 2 resubmitted original applications received during FY 99 within 6 months of receipt.

PDUFA II also established procedural and processing goals beginning in FY 1999. The FY 1999 procedural and processing goals were:

Performance Area	Activity	Performance Goal	FY 1999 Performance*
Meeting Management	Meeting Requests – Notify requestor of formal meeting in writing (date, time, place, and participants).	70% within 14 days of receipt of request.	72%
	Scheduling Meetings – Schedule meetings within goal date or within 14 days of requested date if longer than goal date.	Type A Meetings- 70% within 30 days of receipt of request. Type B Meetings- 70% within 60 days of receipt of request. Type C Meetings- 70% within 75 days of receipt of request.	89%
	Meeting Minutes – Agency prepared minutes, clearly outlining agreements, disagreements, issues for further discussion and action times will be available to sponsor.	70% within 30 calendar days of meeting.	87%
Clinical Holds	Response to sponsor's complete response to a clinical hold.	90% within 30 days of receipt of sponsor's response.	94%
Major Dispute Resolution	Response to sponsor's request for evaluation of protocol design.	70% within 30 days of receipt of sponsor's appeal.	100%
Special Protocol Question Assessment and Agreement	Response to sponsor's request for evaluation of protocol design.	60% within 45 days of receipt of protocol and questions.	None received
Electronic Applications and Submissions	Paperless application processing.	Agency to develop and update information systems to allow paperless receipt and processing of INDs, human drug applications, and related submissions by the end of FY 2002.	
Additional Procedures	Simplification of Action Letters	Centers to amend regulations and processes to provide for issuance of "Approval" (AP) or "Complete Response" (CR) action letters.	
	Sponsor Notification of Deficiencies in Applications.	Centers to notify sponsors of deficiencies via "information request" (IR) when each discipline has finished its initial review.	

*As of October 13, 1999

The Prescription Drug User Fee Act established performance goals for the evaluation of applications for marketing drug and certain biological products. Review performance monitoring is being done in terms of cohorts, e.g., the FY 99 cohort includes applications received from October 1, 1998 through September 30, 1999. Accomplishment of the cohort-year performance goals is not immediately measurable at the close of the fiscal year. The outcome can be measured either 6 or 12 months after the last submission received in FY 99, depending upon the category of submission. Performance goals of the Act began with FY 94. CBER has met or exceeded its performance goals in FY 94 through FY 98. The table below shows CBER's performance on the PDUFA FY 98 cohort. The data provided are as of September 30, 1999.

CBER Review Performance
FY 1998 Cohort of User Fee Applications

Application Type	**Number**			**Percent of Actions**	
	Submitted	Filed	RTF, UN, or WF	Within Goal	Overdue
New Product Standard	6	4	2	100%	0%
New Product Priority	8	8	0	100%	0%
Efficacy Supplements Standard	9	9	0	100%	0%
Efficacy Supplements Priority	1	1	0	100%	0%
Manufacturing Supplements Prior Approval	224	223	1	99%	1%
Manufacturing Supplements CBE & CBE 30	148	148	0	99%	1%
Resubmissions Class 1	5	N/A	N/A	100%	0%
Resubmissions Class 2	16	N/A	N/A	100%	0%

RTF = Refuse to File; UN = Unacceptable for filing (User Fee not paid); WF = Withdrawn before filing; CBE = Change being effected immediately; CBE 30= Change being effected after 30 days; NA = Not applicable.

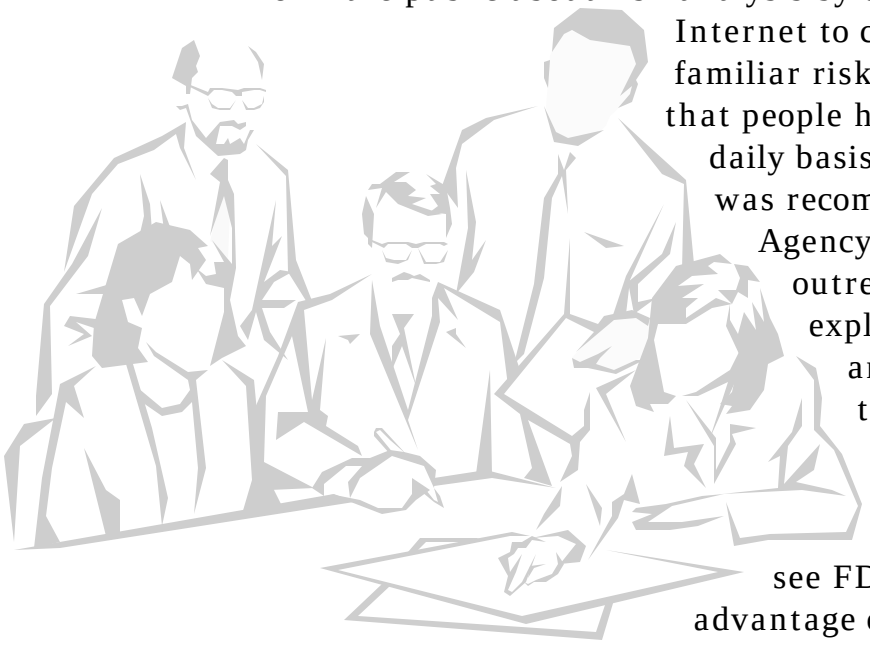
The FY 98 first-action performance goal is to review and issue a comprehensive action letter within goal on at least 90 percent of the new product applications, effectiveness supplements, manufacturing supplements and resubmissions submitted and filed during FY 98. This means that not more than 10 percent of new product applications, effectiveness supplements, manufacturing supplements and resubmissions received and filed during FY 98 should be overdue. Overdue is defined for standard new product and standard effectiveness supplements as having not issued a comprehensive action letter within 12 months of receipt and filing of the application. Overdue is defined for priority new product, priority product supplements, manufacturing supplements and resubmissions as having not issued a comprehensive action letter within 6 months of receipt and filing of the application. The statute allows three additional months for review of original NDA, PLA, BLA, or ELA submissions that involve major amendments within the last three months of their usual review intervals.

The FDA's Center for Biologics Evaluation and Research (CBER) continued to improve the speed of its processes while completing major approvals covering a broad spectrum of new products, technologies, manufacturing methods, indications and premarket applications in FY 1999.

Stakeholder Meetings

CBER held stakeholder meetings on April 28, 1999, in Boston, Massachusetts, and San Francisco, California. Speakers representing the blood, pharmaceutical, devices, and biologics industries made formal presentations. Perhaps one of the most important themes emphasized at these meetings was the importance of a strong science base to ensure sound and timely regulatory decisions. A strong science base is crucial if the Agency is to meet its mission of bringing new technological products to the

market rapidly while ensuring their safety and efficacy. Risk/benefit analysis emerged as a concern in both meetings. It was suggested that the Agency could better inform the public about risk analysis by utilizing the Internet to convey more familiar risk/benefit choices that people have to make on a daily basis. In addition, it was recommended that the Agency develop an outreach program that explains risk/benefit analysis in simple terms.



Some indicated they would like to see FDA/CBER take advantage of industry resources to expand its own scientific knowledge base, through efforts such as vendor days (Vendor day is a technique designed to gain knowledge and interaction with industry.) and co-sponsored educational workshops.

Implementation of Phase 1 of the Managed Review Process

On August 1, 1999, CBER implemented Phase 1 of its expanded and enhanced Managed Review Process. The Managed Review Process was designed by CBER personnel and is the first step in meeting our strategic vision of "a managed and integrated regulatory process which is continuous from discovery to post marketing." A strategy utilized to reach this goal is to apply the principles of managed review to the entire regulatory process. Managed review principles include the design of a review process which is streamlined, consistent, and efficient.

During the design phase of this process, the Managed Review Committee identified five phases of CBER's regulatory process: Pre-Submission, Investigational, Applications/Supplements, Post-Marketing, and Cross-Cutting. Each of these phases contains regulatory activities specific to that phase of drug development and review, except for Cross-Cutting which includes regulatory activities that encompass all phases – from Pre-Submission to Post-Marketing. Implementation of Phase 1 consists of the Pre-submission [(pre-Investigational New Drugs (INDs) and pre-Investigational Device Exemptions (IDEs)] and investigational (INDs/IDEs) phases, and the Coordinate Public Health Based Research subphase. These phases begin with the initial contact from a sponsor or investigator seeking information from the Center and concludes with the submission of the marketing application or supplement.

Beginning August 1, 1999, two changes were made to CBER's regulatory process: the selection of Regulatory Project Manager and the establishment of review target dates. The Regulatory Project Manager is a member of the review team who is responsible for coordinating and facilitating the review of regulatory submissions. The review target dates are deadlines for review activities, that when met, lend themselves to moving the review process forward. These review target dates are not mandated milestones – they contain some flexibility and are negotiated by the review team.

In the near future, Phases 2 and 3 of this process will be implemented. Phase 2 consists of the Application/Supplement phase and Phase 3, Post-Marketing and any Cross-Cutting activities not yet implemented.

International Activities

CBER Collaboration with World Health Organization (WHO) and Pan American Health Organization (PAHO)

In FY 1999, CBER has continued its support of WHO headquarters and the Americas Regional Office Of WHO (PAHO). CBER has provided technical support/training, scientific expertise, and representation to numerous WHO technical working groups, consultative groups, and scientific meetings. These working group meetings covered topics such as:

1) Vaccines and other product standards, controls, use and research issues

2) Cytokines which included the 4th Annual WHO International Consultation on Cytokine Standards

3) Vaccine Regulatory Issues which included the PAHO Workshop on Vaccine Licensing and Lot Release for National Control Authorities in Latin America, Informal Consultation of Experts on National Regulation of Vaccines, and Expert Committee on Biological Standardization Meeting

4) Future directions, which included the first meeting of interested parties to the Health Technology and Pharmaceuticals Cluster, Children's Vaccine Initiative 1998 Consultative Group Meeting, Workshop to discuss the potential for Harmonization of Technical Requirements for Vaccine Production Quality and Licensing, and the 9th International Conference of Drug Regulatory Authorities.

International Harmonization

The International Conference on Harmonization (ICH) Steering Committee and Expert Working Groups (EWGS) met in March 1999. The next major ICH Conference is scheduled for November 2000 in San Diego, California.

In FY1999, some important documents were produced with substantial CBER input.

- The guideline, "Specifications for Biotechnological and Biological Products" was implemented.

- The contract organization to implement the Medical Dictionary for Regulatory Activities (MedDRA), Maintenance and Support Services Organization (MSSO) successfully launched the ICH Medical Dictionary in March 1999.

CBER/NIBSC FY 1999 Activities

The National Institute of Biological Standards And Control (NIBSC)/CBER research collaboration agreement was signed and research collaboration discussions began. The second meeting of the research collaboration working group was held July 1999, at the NIBSC in London, England.

United States/European Community (EC) Mutual Recognition Agreement (MRA)

CBER continues to play a role in the implementation of the MRA between the United States and the EC. The MRA was signed in May 1998 and entered into force in December 1998 with an exchange of letters between the United States and EC. CBER participates in the implementation teams for both the pharmaceutical GMP and the medical device annexes of the MRA.

CBER participated in the first formal meeting of the MRA Joint Sectoral Committee (JSC) for the pharmaceutical GMP annex, which was held in Rockville in May 1999. This was the first meeting of the Pharmaceutical Good Manufacturing Practice (GMP) JSC. At the meeting, the Terms of Reference document was agreed to in principle. This document describes the way in which the JSC will operate. The parties also began a preliminary discussion about confidentiality issues, which will have a major impact on the information exchanges necessary to fully implement the agreement.

Other International Initiatives

- CBER participated in the 3rd Symposium on Hematopoietic Stem Cell Transplantation which addressed the international effort to develop a worldwide network of cord blood banks with an associated set of minimal standards.

- CBER continues to communicate and work with the international community in order to develop a regulatory framework for Xenotransplantation. A CBER representative participates in the electronic regulatory forum of the Organization for Economic Cooperation and Development (OECD).

- CBER participated in an International Forum on Regulation of Human Tissue Engineered Products held on October 29, 1998. Regulators from around the world met to share information on international activities concerning these products. In addition, they discussed regulatory initiatives and problems faced in developing them.

- CBER participated in a meeting with Canada and Mexico as part of the Canada-United States-Mexico Compliance Information Group, held in Ottawa, Canada in October 1998. The group focused on compliance-related issues. Some topics that were addressed by the group include information exchange, with a focus on

confidentiality; joint inspections; and development of a list of regulatory terminology.

Emerging Infectious Diseases

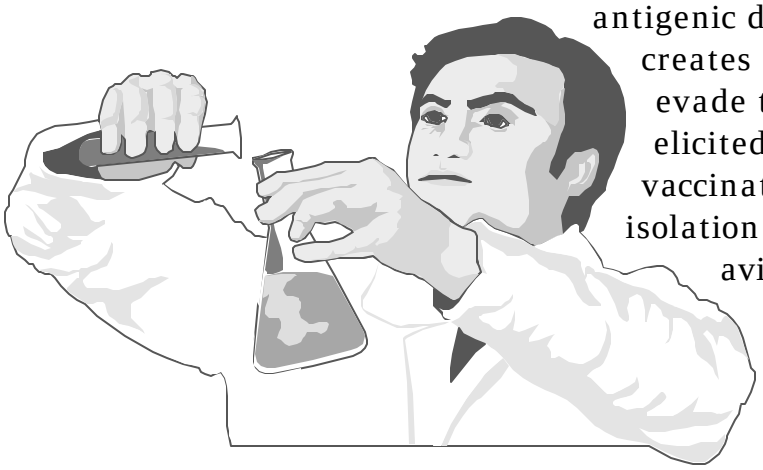
Judicious use of antimicrobial drugs in human medicine through labeling and marketing controls, as well as provider and patient education, may be the most important mechanism to control the emergence of antimicrobial drug resistant bacteria. CBER is addressing this global problem through active participation in the FDA-wide Antimicrobial Resistance Task Force, which is defining mechanisms to expedite research, review, and licensure of novel products as alternatives to antibiotic therapy.

One approach to addressing emerging antimicrobial resistance may be through the development of vaccines against resistant organisms. Two aspects need to be considered: the imminent threat to the public health from those organisms which have already developed multidrug resistance; and the future threat of increased antimicrobial resistance due to the inappropriate use of antimicrobials in treating "common" diseases such as otitis media (OM) and urinary tract infections. CBER is addressing both of these public health threats through product specific research and review, and development and implementation of regulatory mechanisms to streamline the review process from development through approval.

In addition to the development of vaccines for expanded use in at-risk populations, the re-emergence of organisms as threats to the public health also requires attention. For example, tuberculosis (TB) is a disease that is rising in importance as a public health threat due to the increasing prevalence of multi-drug resistant organisms. CBER is active in research regarding the mechanisms of antibiotic resistance and alternative vaccine strategies for development of new TB vaccines, as well as expanding the

expertise in reviewing these novel products. CBER was instrumental in the discussions and drafting of the interagency "Blueprint for Tuberculosis Vaccine Development" which provides recommendations for developing a national strategy for development of effective TB vaccines.

Similarly, as organisms undergo environmental and genetic changes, previously effective vaccines may no longer protect against the new variant. For example, antigenic drift of influenza viruses creates new variants which can evade the immune responses elicited by previous vaccinations. In addition, isolation of viruses such as the avian influenza viruses that are associated with higher rates of mortality pose important public health risks. Research conducted in the area of influenza virus molecular biology and pathogenesis allows CBER to play a role in the coordinated public health response to the outbreaks of avian influenza virus abroad.



Blood supplies are constantly exposed to the dangers posed by new blood borne pathogens for which there are no vaccines or adequate therapies. These pathogens include HIV, Hepatitis B and C, human T-lymphotropic virus (HTLV) I & II, Cytomegalovirus (CMV), Transmissible Spongioform Encephalopathies and others. Most of the pathogens that have been recently implicated are viral or viral-like (prions) in nature and present great challenges to devising therapeutic treatment and prophylactic vaccines. Many of these infectious agents have the ability to integrate into the chromosomes of human somatic and germ-line cells. Because most of these blood borne contaminants have successfully evaded therapeutic and vaccine strategies, the current strategy for protecting the public health is to test and disqualify donors and blood

donations found to be contaminated with known pathogens. As newer pathogens (viruses, parasites, prions) enter the pool of donors and contaminate the blood supply, new strategies to test donors, whole blood, blood plasma, and other blood derivative products need to be developed. The strategies could include Polymerase Chain Reaction (PCR) screening assays, the new microarray technology, to quickly and accurately detect viral, bacterial, nanobacterial, and prion contaminants.

Transplantation of animal tissues and organs into humans raises great concern about importing pathogens into human recipients that had been formerly restricted to animals. Persons becoming infected from xenotransplantation could disseminate the pathogens to other people through personal contacts. CBER has been at the forefront of identifying potential animal pathogens that can replicate in humans, such as endogenous retroviruses, and developing screening tests for use on animal tissues and organs intended for use in humans. As with blood borne contaminants, many of the newly identified xenotransplantation contaminants may be viruses or prions for which there are no therapies or vaccines and which may integrate into somatic and germ-line cells. Critical research needs to be carried out to identify the presence of endogenous retroviruses and to establish essential monitoring programs for xenotransplantation recipients. FDA will need to provide the standards and methods which each sponsor will be held to for the screening of animal tissue and organs and the long-term monitoring of xenotransplantation patients.

Compliance Update

Regulatory Highlights

Regulatory actions support the broad goals of safeguarding the public health and ensuring honesty and fair dealing between regulated industry, FDA, and consumer. In FY 99, CBER pursued a number of significant regulatory actions. In summary, CBER pursued license revocations in five cases, took one seizure action, and issued or concurred in 27 warning letters. In addition to new actions, CBER continues to monitor the progress of firms that were subject to injunction in previous years. Some of these cases are summarized below.

Note: The information contained in this section reflects the status of the subject firms as of the end of FY 99 (September 30, 1999). It does not include any actions that may have taken place subsequent to that time. It is also not an exhaustive list of actions taken in FY 99.

Injunctions

- *Alpha Therapeutic Corporation (Alpha)*

Since entering into the Consent Decree in February 1998, there have been numerous correspondences between Alpha Therapeutic Corporation (Alpha) and FDA. In FY 1999, Alpha was ordered on two occasions to recall all products manufactured at their South Filling area from December 1997 to June 1998 due to manufacturing deficiencies and unsanitary conditions in the manufacturing facility.

FDA continued to monitor progress during FY 1999. In June and July 1999, two Orders were issued to cease distribution of products from the South and North Filling stations pending the Agency's complete review of inspectional findings. In addition, lot release of Alpha's products was suspended.

- *American Red Cross (ARC)*

The FDA continues to monitor the ARC's compliance status regarding the May 12, 1993, Consent Decree of Permanent Injunction. During FY 1999, the ARC completed the Consent Decree requirements related to the Donor Deferral Register (DDR) audit, which were the last outstanding requirements of the Decree. In addition, the FDA informed the ARC that the corrective actions taken regarding the February 9, 1998, Consent Decree Section VI.A. letter, citing employee training deficiencies were acceptable. As of the end of FY 99, the requirements of all previously issued VI.A. letters have been satisfied.

- *Blood Systems, Inc. (BSI)*

BSI has completed all requirements for submissions under the Consent Decree (entered into on April 22, 1996) and continues to submit Internal Audit Summary Reports to the FDA every six months. FDA continues to monitor BSI's compliance status through review of the audit reports and inspection of its facilities.

FDA has inspected the majority of the licensed BSI facilities and fixed-site donor centers since the entry of the Decree. FDA has not issued any letters pursuant to section VI.A. of the Consent Decree as a result of these inspections.

- *Centeon L.L.C. (Centeon)*

Centeon entered into a Consent Decree of Permanent Injunction in January 1997. The firm was inspected in FY 98 and numerous deviations from current GMPs were noted. FDA issued a letter to the firm under the terms of the Consent Decree, notifying the firm to immediately cease manufacturing, processing, packing, holding and distributing all biological and drug products manufactured at its Bradley, IL facility, with the exception of those products determined by FDA to be medically necessary. The letter outlined the corrective actions the firm must take, including obtaining a third party consultant and increasing the quality assurance oversight for manufacturing. A comprehensive inspection of the firm was conducted from June to September 1999. As of the end of FY99, the inspection findings were still being reviewed by the Agency.

- *Parkedale Pharmaceuticals, Inc.*

In August 1999, FDA's Detroit District Office issued an Order under the Consent Decree of Permanent Injunction to Parkedale, Rochester, MI. Parkedale is a successor company to the Warner-Lambert Company, and is subject to the terms of the Consent Decree entered into in August 1993 by Warner-Lambert. The Order was based on violations documented during inspections performed in May and August 1999. Parkedale was ordered to cease distribution of all lots of Histoplasmin pending performance and FDA review and acceptance of product tests. The Order also informed Parkedale that the firm's overall corrective action plan is incomplete. Following receipt of the Order, Parkedale voluntarily surrendered its license for Histoplasmin.

Seizures

In FY 1999, there was one seizure action for biological products.

- Immune Globulin Intravenous manufactured by the Korea Green Cross Corporation was seized. Approximately twenty cases of Immune Globulin Intravenous located in Miami, Florida, and manufactured by the Korea Green Cross Corporation were seized by the U.S. Marshals Service. The product did not have approval for distribution/use in the United States, nor was the product subject to an investigational new drug application (IND). While an IND application was filed for the product, it was not approved. The product was inappropriately distributed and used in humans. The seized product was subsequently destroyed.

Advertising and Promotional Labeling

During FY 1999, CBER reviewed 3,784 events involving advertising and promotional material. These included 3,191 routine submissions of advertising and promotional materials for record purposes made at the time of publication for dissemination of licensed biologic products, and 403 submissions of proposed new advertising and promotional materials for advisory comments. An additional 76 submissions were associated with new campaigns (logos, trade names, etc.). A total of 114 complaints were received, most of which involved allegations of false and misleading claims, donor incentive inquiries, pre-approval advertising, and related advertising and promotional problems associated with INDs.

FDA Concerns Regarding Products Manufactured by Abbott Laboratories

FDA informed Abbott Laboratories of concerns related to manufacturing deficiencies for urokinase (Abbokinase). Further distribution of Abbokinase was halted until these problems are corrected. FDA's concerns about the product relate to serious deficiencies in the manufacturing process, the testing of the product, and the screening and testing of the kidney cell donors used to make Abbokinase. Like other products manufactured using human source material, Abbokinase has the potential to transmit infectious agents.

During inspections of Abbott Laboratories and BioWhittaker, Inc., Abbott's supplier of human kidney cells, FDA identified numerous significant deviations from current good manufacturing practice (CGMP) regulations.

In January 1999, FDA issued a letter to health care providers alerting them about important safety information regarding the use of Abbokinase. The letter included: 1) information about the potential to transmit infectious agents; and 2) a recommendation that Abbokinase be reserved only for those situations where the physician has considered other available treatment alternatives and has determined that the use of Abbokinase is critical to the care of a patient in a specific situation. Upon FDA's request, Abbott revised the labeling of the product to include additional information on safety concerns so physicians would have a clear understanding of the risks associated with Abbokinase.

In a July 14, 1999, letter to Abbott Laboratories, the FDA concluded that it is not prepared to exercise its enforcement discretion regarding Abbott's distribution of

Abbokinase unless and until Abbott takes steps to ensure that the product is safe. In addition, FDA advised Abbott that it is critical the firm reviews and redesigns, where necessary, the manufacturing process for Abbokinase in order to comply with current good manufacturing practices.

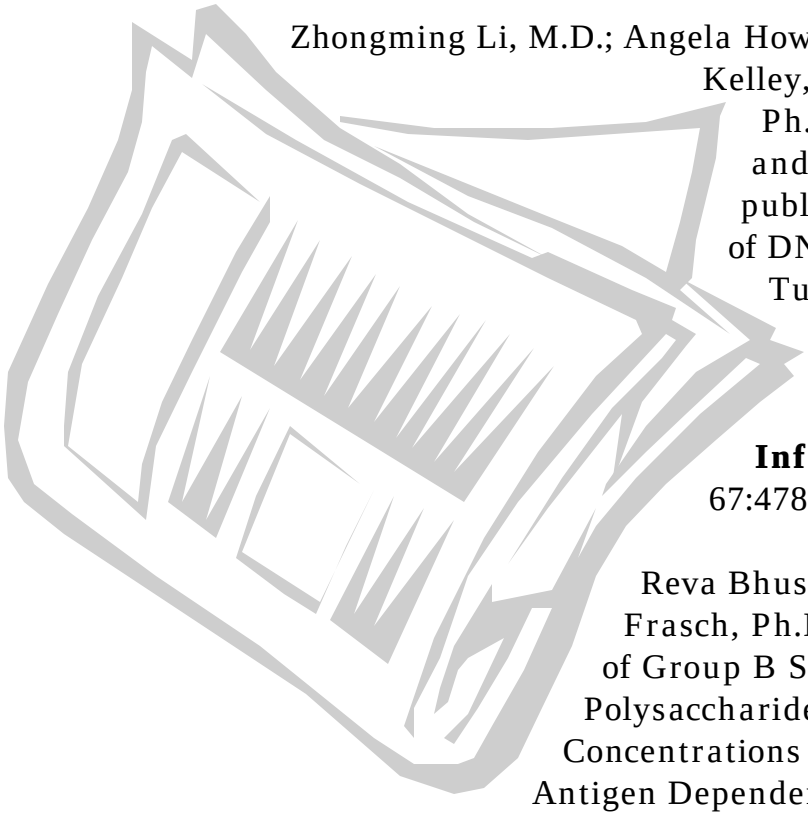
Team Biologics

Since the implementation of Team Biologics in 1997, the Office of Compliance and Biologics Quality (OCBQ) continues to be actively involved in the program. The implementing document established a schedule for transferring CBER post-approval inspections to the field organization. Responsibility for inspections of licensed allergenic and therapeutic products was transferred to Team Biologics in the beginning of FY 1999. The transfer of the final products is expected to follow in FY 2000. In FY 1999, OCBQ finalized the compliance programs for the allergenic and licensed therapeutic product inspections.

Training was held for the Team Biologics Core Team, Compliance Officers, and Product Specialists in vaccines. In addition, a blood bank training course was given to the Team Biologics blood cadre investigators.

CBER Research Publication Highlights

Scott Stibitz and Mei-Shin Yang published “Genomic Plasticity in Natural Populations of *Bordetella pertussis*” in the **Journal of Bacteriology**, September, 1999.



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Arifa S. Khan, Ph.D.; Johnna Sears, M.S.; Jacqueline Muller, Ph.D.; Teresa A. Galvin, Ph.D.; and Muhammad Shahabuddin, Ph.D. published “Sensitive Assays for Isolation and Detection of Simian Foamy Retroviruses” in **Journal of Clinical Microbiology**, 8:2678-2686, Volume 37, August 1999.

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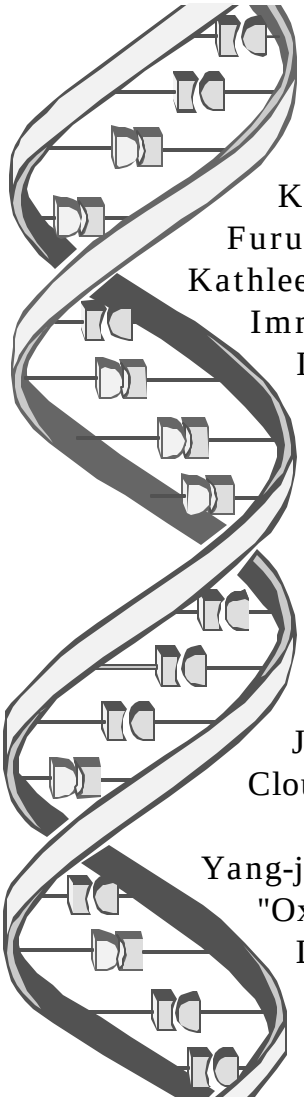
Karen L. Elkins, Ph.D.; T. R. Rhinehart-Jones; Scott Stibitz; Jacqueline S. Conover; and Dennis M. Klinman, M.D.,Ph.D. published “Bacterial DNA Protects Mice Against Lethal Infection by Intracellular Bacteria” in the **Journal of Immunology**, 162:2291, 1999.

Richard W. Pastor, Ph.D. and Wabash College scientist Scott E. Feller, Ph.D. published “Constant Surface Tension Simulations of Lipid Bilayers: the Sensitivity of Surface Areas and Compressibilities” in the **Journal of Chemical Physics**, July, 1999.

Robert Duncan, Ph.D.; Jacqueline Muller, Ph.D.; Nancy Lee, M.S.; Ali Esmaili; and Hira L. Nakhasi, Ph.D. published “Rubella Virus-induced Apoptosis Varies Among Cell Lines and is Modulated by Bcl-Xl and Caspase Inhibitors” in **Virology**, 255, 117-128, 1999.

Richard Kenney, M.D.; Albert Gam; and Kamela Evans-Davis, D.V.M. in collaboration with scientists from NIH (David Sacks, Ph.D.); Genetics Institute (Joseph Sypek, Ph.D.); and Biobras, Brazil (Luciano Vilela, Ph.D.) published “Protective Immunity Using Recombinant Human IL-12 and Alum as Adjuvants in a Primate Model of Cutaneous Leishmaniasis” in the **Journal of Immunology**, 163:4481-8, 1999.

Robert Boykins, Sherwin Lee, Indira Hewlett, Ph.D. and Subhash Dhawan, Ph.D. in collaboration with NIH scientists Renaud Mahieux, Ph.D., Uma Shankavaram, Ph.D., Yong S. Gho, Ph.D., Larry Wahl, Ph.D., Hynda Kleinman, Ph.D., John Brady, Ph.D., Kenneth Yamada, M.D., Ph.D. published " Cutting Edge: A short polypeptide domain of HIV-1-Tat protein mediates pathogenesis" in the **Journal of Immunology,** 163, 15-20, 1999.



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Pablo A. Garcia-Ojeda, Ph.D.; Kathryn E. Stein, Ph.D.; and former CBER scientist Leonard J. Rubinstein in collaboration with current and former scientists from the National Research Council of Canada Harold J. Jennings and Francis Michon published "Murine Immune Responses to *Neisseria meningitidis* Group Capsular Polysaccharide and a Thymus-dependent Toxoid Conjugate Vaccine" in **Infection and Immunity**, 66:5450-5456, 1998.

Andrzej Wilk, Ph.D.; Andrzej Grajkowski, Ph.D.; and Serge L. Beaucage, Ph.D. in collaboration with National Cancer Institute scientist Lawrence R. Phillips, Ph.D. published "Deoxyribonucleoside Cyclic *N*-Acylphosphoramidites as a New Class of Monomers for the Stetreocontrolled Synthesis of Oligodeoxyribonucleoside Phosphorothioates" in the **Journal of the American Chemical Society**, December, 1999.

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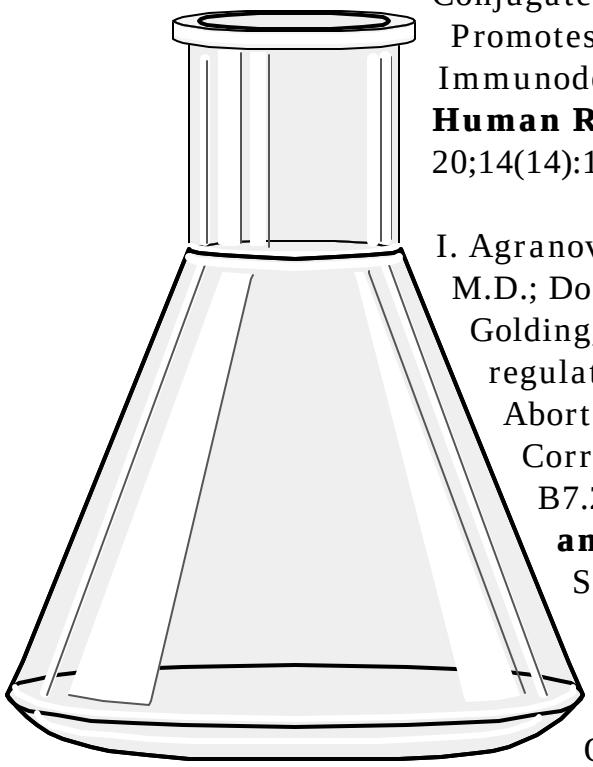

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Harold Dickensheets, Ph.D. and Raymond Donnelly, Ph.D. in collaboration with scientists at Tularik, Inc. (Chandrasekar Venkataraman, Ph.D., and Ulrike Schindler, Ph.D. published: “Interferons Inhibit Activation of STAT6 by Interleukin-4 in Human Monocytes by Inducing SOCS-1 Gene Expression” in the **Proceedings of the National Academy of Sciences, USA** (1999) 96:10800-10805.

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Cheryl K. Lapham, Ph.D.; Marina B. Zaitseva, Ph.D.; Shirley Lee, M.D.; Tatiana Romantseva, M.S.; and Hana Golding, Ph.D. published "Fusion of Monocytes and Macrophages with HIV-1 Correlates with Biochemical Properties of CXCR4 and CCR5" in **Nature Medicine** 5:303-308, 1999.

Nga Yen Nguyen, Ph.D.; John Bernard Ewell; and National Cancer Institute scientists Ruoli Bai, Ph.D.; and Ernest Hamel, Ph.D. published “Direct Photoaffinity Labeling of Cysteine-211 or a Nearby Amino Acid Residue of ß-Tubulin by Guanosine 5’-Diphosphate Bound in the Exchangeable **Journal of Biological Chemistry**:274(18), 12710-12714, 1999.

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M. Christine Anderson and scientists from USDA, Johns Hopkins University, and the Environmental Protection Agency R.J. Brenner, Ph.D.; D.A. Focks, Ph.D.; E. Horowitz; A. Togais, M.D.; R. Kramer, Ph.D.; G. Williams, Ph.D.; G. Weichman, Ph.D.; and D. Milne published, "Spatial Environmental Assessment and Mitigation of German Cockroaches and Allergens using Polyclonal Detection Assays and Precision Targeting Software," in

Proceedings of the Int'l Conf. On Urban Pests, Prague Czech Republic, 184-194 (1999).

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Appendix: List of Major Approvals

NEW PRODUCTS

Proper Name ***(Trade Name)***	**Manufacturer**	**Indications for Use**
Etanercept ***(Enbrel)***	Immunex Corporation Seattle, WA	Treatment of rheumatoid arthritis in patients who have had an inadequate response to one or more disease modifying antirheumatic drugs (DMARDS)
Lyme Disease Vaccine (Recombinant OspA) ***(LYMErix)***	SmithKline Beecham Biologicals Rixensart, Belgium	Active immunization against Lyme disease in individuals aged 15-70 years
Anti-thymocyte Globulin (Rabbit) ***(Thymoglobulin)***	Pasteur Merieux Serums et Vaccins, S.A. Lyon, France	Immunosuppressive therapy for the treatment of acute allograft rejection and prevention of recurrent acute allograft rejection in renal transplant patients

NEW PRODUCTS

Proper Name ***(Trade Name)***	**Manufacturer**	**Indications for Use**
Denileukin diftitox ***(Ontak)***	Seragen, Inc. Hopkinson, MA	Treatment of persistent or recurrent cutaneous T-cell lymphoma (orphan designation)
Hepatitis B Immune Globulin (Human) ***(Nabi-HB)***	Nabi Boca Raton, FL	For acute exposure to blood containing HbsAg; perinatal exposure of infants born to HbsAg-positive mothers; sexual exposure to HbsAg-positive persons, and household exposure of infants to persons with acute HBV infection
Interferon alfa-n1 (Lymphoblastoid) ***(Wellferon)***	Wellcome Foundation Limited Welcome Research Laboratories Beckenham, Kent United Kingdom	Treatment of Hepatitis C in patients 18 years of age or older without decompensated liver disease
Coagulation Factor VIIa (Recombinant) ***(NovoSeven)***	Novo Nordisk A/S Bagsvaerd, Denmark	Treatment of bleeding episodes in hemophilia A and B patients with inhibitors to Factor VIII or Factor IX

NEW PRODUCTS

Proper Name ***(Trade Name)***	**Manufacturer**	**Indications for Use**
Antihemophilic Factor/von Willebrand Factor Complex (Human) ***(Humate-P)***	Centeon Pharma GmbH Marburg, Germany	Prevention and control of hemorrhagic episodes in hemophilia A patients, new indication for treatment of von Willebrand disease
Hextend, High Molecular Weight Hydroxyethyl Starch 6% (Hetastarch) in Electrolyte Dextrose Solution ***(Hextend)***	Bio Time, Inc. Berkeley, CA	Plasma volume expander for treatment of hypovolemia during surgery
Abbott Prism	Abbott Laboratories Abbott Park, IL	First fully automated system for high volume blood screening, can process up to 960 tests per hour with multiple channels to accommodate individual screening assays
Isolex 300 Magnetic Cell Separation System	Nexell Therapeutics, Inc. Irvine, CA	For processing autologous peripheral blood progenitor cell (PBPC) products to obtain CD34+ cell enriched population intended for hematopoietic reconstitution after myeloblative therapy in patients with CD34-negative tumors

NEW PRODUCTS

Proper Name ***(Trade Name)***	**Manufacturer**	**Indications for Use**
DACS™SC	Dendreon Corporation Seattle, WA	For processing autologous mobilized peripheral blood progenitor cells (PBPC) collected by leukapheresis to reduce red blood cells, platelets and granulocytes in the final PBPC product

SUPPLEMENTS

Proper Name ***(Trade Name)***	**Manufacturer**	**Indications for Use**
BCG Vaccine ***(Mycobax)***	Connaught Laboratories Limited North York, Ontario Canada	**Expanded Indication:** For immunization against tuberculosis
Human Immunodeficiency Virus Type 1 (Western Blot) (Genetic Systems HIV-1 Western Blot)	Genetics Systems Corporation Redmond, WA	**New Indication:** New HIV-1 Western Blot assay intended for use with persons of unknown risk as more specific test on human serum, plasma, or dried blood specimens found to be repeatedly reactive using screening procedure
Cytomegalovirus Immune Globulin Intravenous (Human)	Massachusetts Public Health Biologic Laboratories Boston, MA	**New Indication:** For use in solid organ transplants – kidney, lung, liver, pancreas and heart
Immune Globulin Intravenous ***(None)***	Baxter Healthcare Corporation Glendale, CA	**New Indication:** For treatment of Kawasaki Disease in conjunction with high dose aspirin (80-100 mg/kg/day in four divided doses

SUPPLEMENTS

Proper Name ***(Trade Name)***	**Manufacturer**	**Indications for Use**
Hepatitis C Virus Encoded Antigen (Recombinant/ Synthetic (RIBA))	Chiron Corporation Emeryville, CA	**Improved Test:** A more specific supplemental test to detect antibodies to Hepatitis C Virus in human serum or plasma
Etanercept ***Enbrel***	Immunex Corporation Seattle, WA	**New Indication:** To include the treatment of polyarticular course juvenile rheumatoid arthritis (JRA)
Reagent Red Blood Cells ***(Olympus PK Reagent Red Blood Cells)***	Gamma Biologicals, Inc. Houston, TX	**New Reagent:** Reagent specifically dedicated for automated instrument
Hepatitis B Vaccine ***(Recombivax)***	Merck & Co., Inc. West Point, PA	**Manufacturing Change:** Preservative-free pediatric/adolescent product